

Tracts 1866 C



A STUDY OF THE HUMAN PLACENTA, PHYSIOLOGICAL AND PATHOLOGICAL.

By THOMAS WATTS EDEN, M.D., M.R.C.P., *Physician to Out-Patients,
Chelsea Hospital for Women.*

*From the Laboratories of the Conjoint Board of the Royal Colleges of Physicians (Lond.)
and Surgeons (Eng.).*

(PLATES XIX. to XXII.)

PART I.—DEVELOPMENT AND NORMAL STRUCTURE.

THE object of this paper is to give some account of the minute structure of the human placenta, with especial reference to its development. For the sake of brevity, a description of the macroscopic characters of the placenta is omitted, and some of the better known points of histology are only briefly alluded to.

For reasons which will afterwards appear, the normal structure of the placenta must be studied in specimens obtained not later than the mid-term of gestation. This paper is therefore not concerned with the placenta at the full term. Frequent references are made to the very voluminous literature of the subject, and a list of all such references will be found at the end of the paper.

The placenta consists of two distinct series of structures; one developed from the ovum, *the fetal placenta*; the other developed from the uterus, the *maternal placenta*. The two parts, of which the placenta is composed, are best studied separately.

A. *The Fœtal Placenta.*

The fœtal placenta is an elaboration of the outer fœtal envelope or chorion; it is therefore necessary, in the first place, to trace briefly the development of this membrane.

Very few facts are known concerning the development of the human ovum, during the first 14 days of its existence. Reichert⁽³⁶⁾¹ and His⁽¹³⁾ have described human ova of about 12–13 days; in them the decidua reflexa was fully formed, and chorionic villi

¹ The numbers in brackets refer to the Bibliography at the end of the paper.

were present over the greater part of the surface of the ovum. By what precise steps this stage is reached, in man, is not known. We can only assume that it is by a process which does not materially differ from that of mammals lower in the scale than man. We therefore conclude that two structures are chiefly concerned in the formation of the human chorion—(1) the *zona pellucida* or primitive envelope of the ovum, and (2) the *subzonal membrane*, or *false amnion*, which is applied to the inner surface of the *zona pellucida*, forming a complete sphere within it. The latter envelope is formed, together with the true amnion, from the extra-embryonic portion of the somatopleure. It is composed of an outer epiblastic and an inner mesoblastic layer. Kölliker (²¹).

There has been great conflict of opinion upon the relations of the allantois to the chorion. The old view was that the allantois grew out from the posterior end of the primitive alimentary canal to the wall of the ovum, in the form of a hollow process, surrounded by mesoblastic tissue; that a direct connection was thus established between the embryo and the envelope, and that along this bridge vessels developed from the terminal bifurcations of the aorta, which vascularised the chorion. This view has recently been opposed by His, and in point of fact there are no direct observations to support it. His (¹³) points out, among other objections to the theory, that allantoic or umbilical vessels have been found reaching the chorion by a mesoblastic stalk at a period when the allantois itself is only beginning to appear. Without entering into the discussion further, the view of His may be briefly stated, and adopted as most in accord with the facts as they stand at present.

The old view assumed that, after the closure of the amnion, a connection was established between the embryo and the wall of the ovum by the outgrowth of the allantois. His believes that by the closure of the amnion the fœtus is not entirely separated from its envelopes, but remains in connection with them through a bridge of mesoblastic tissue, which is continuous with its posterior extremity. This bridge he terms the *ventral stalk*. Along it the umbilical vessels grow to reach the chorion. At a later period the allantois grows out towards the chorion, in contact with the ventral stalk; but it never quite reaches the wall of the ovum. It participates with the ventral stalk and the umbilical vessels in the formation of the umbilical cord.

The chorion is thus derived from the embryonic epiblast and mesoblast layers; the epiblast forms the epithelial layer covering the entire membrane and its villi; the mesoblast forms the connective tissue stroma supporting the vessels. The *zona pellucida* probably disappears early.

In the earliest specimens of the human ovum which have been carefully examined (about the end of the second week), villi were found over nearly the entire surface of the chorion; they, therefore, probably appear at a very early period. They are formed, in the first place,

as simple ectodermal buds, which grow by a process of repeated branching, and are arborescent when fully formed. In Reichert's ovum, the villi were not found covering the entire surface (³⁶). His found them fairly evenly distributed (¹³). There is, at this period, no trace of the differentiation of a special area to form the placenta. Many of the villi are vascularised in all parts of the ovum.

This represents all that is at present known of the development of the chorionic membrane in man. It is closely related to the development of one of the maternal envelopes of the ovum, the decidua reflexa. In a human ovum of the end of the second week, the reflexa has closed completely over the ovum, and the chorionic villi are embedded in it, but so lightly that the two are readily separable. Observations are greatly needed as to the precise relations of the villi to the decidual tissues at this period; beyond the fact that there is a delicate union between them we know nothing. It is, however, a fact of great physiological importance, that, by the end of the second week, the foetal and maternal vessels are brought into close relations by the embedding of the villi in maternal tissues, thus forming what is practically a simple type of placenta in which the wall of the entire ovum is concerned.

The conclusion seems inevitable that the chief function of the decidua reflexa is associated with the nutrition of the ovum. It is a highly vascular membrane, richly supplied with glands, and the foetal vessels enclosed in their delicate villi become buried in its substance. An interchange by osmosis between the maternal and foetal blood must inevitably result. No doubt a secondary function of the reflexa is to support the rapidly growing ovum.

At the end of the second week, therefore, we have in the human ovum a simple form of diffused placenta, corresponding to that which is met with in the sow, the mare, the cetacea, etc. In the mammalia generally the umbilical vesicle plays a comparatively unimportant part in the nutrition of the embryo; and early provision is therefore made for the direct transmission of nutrient materials from the blood of the mother to the embryo. This provision, as we have seen, is found in the embedding of the foetal villi in maternal tissues. In this manner the foetus is nourished, while time is gained for the development of the more highly specialised discoidal placenta. Text-books usually state that the placenta does not appear, in the case of human ovum, till the end of the second month. I am disposed to believe, from specimens which I have examined from the middle of the second month, that the placenta is at that time already in an advanced stage of development. The point, however, is not of great importance, for the development of the discoidal placenta in man, simply consists in the specialisation of a part of the chorion to perform the work which, in earlier stages, is done by the whole of it. At the placental site the villi increase very much in size and number, and in the complexity of their branchings; at the same time important changes, to be afterwards described, occur in the

underlying decidua. As the discoidal placenta develops, the villi covering the general chorionic surface atrophy and become devascularised, and by the end of the second month this process is already complete. A diminution of the total area of the placenta is thus compensated for by the specialisation of a part of it.

It is, therefore, possible to account in a fairly satisfactory manner for the nutrition of the ovum from the end of the second week onwards. One point in this connection must be left over for future consideration, namely, the relative part which is played in the nutrition of the ovum by the glands and by the blood vessels of the maternal tissues. But there remains the important question: How is the ovum nourished during the first two weeks of its existence before the formation of the allantoic circulation? During these two weeks the ovum increases to twenty-five times its original diameter. The suggestion that, as in the case of the Aves, there is stored up in the minute human ovum an amount of nutrient material, sufficient to accomplish these results, seems incredible. The true solution is probably to be found upon quite other lines. A Dutch observer, Hubrecht, has in a recent research ⁽¹⁶⁾ upon the placentation of the hedgehog, thrown a good deal of light upon the question of the early nutrition of the ovum. In the earliest stages of the development of the hedgehog, Hubrecht describes a layer of very vascular spongy tissue surrounding the ovum, which he terms the trophosphere. This trophosphere is formed in part from the ectoderm of the blastocyst, and in part from the adjacent cellular tissue of the decidua. It contains large sinuses full of maternal blood; the outer layer of the foetal ectoderm, as well as the decidual portion, is thus richly supplied with maternal blood. When the vitelline circulation is established, primitive mesoblastic villi are formed, containing branches of the vitelline vessels, which push their way into the tissues of the trophosphere, and thus bring the foetal and maternal blood vessels into close contact. There is in fact, in the hedgehog, a vitelline placenta formed, consisting of a foetal portion with villi, and a maternal portion with large blood sinuses. Later on, as the allantoic circulation develops, the vitelline placenta disappears. It may be, of course, that the vitelline placenta of the hedgehog has no homologue in the human ovum, but Hubrecht's observations are, at least, highly suggestive.

To return now to the formation of the discoidal placenta. During the second month its formation is begun; after the mid-term it undergoes numerous retrograde changes, which will be described in a subsequent paper. The normal structure of the placenta must therefore be studied in specimens taken from the third and fourth months.

At the third or fourth month the foetal placenta consists of a dense forest of tree-like structures, having many complicated branches. Their base of attachment is the wall of the ovum. The villi are the free terminal and lateral buds, and the divisions upon which they grow represent the twigs and branches. In their growth adjacent branches often become

interlaced. The villi of the human placenta are somewhat club-shaped structures, with a rounded apex and a constricted base. Most of them are free; many, however, reach the decidua serotina and become embedded in it, forming a direct union of the foetal and maternal structures of the placenta. No one has attempted to compute the number of villi present in a fully-developed placenta, but it must be very large.

The portion of the chorion concerned in the formation of the placenta is commonly called the *chorion frondosum*; it consists of two parts, a membrane or layer, underlying the amnion, and the branching structures which spring from it. Each part of the chorion frondosum consists of three sets of structures—

1. An outer covering of epithelium.
2. A delicate connective tissue stroma, supporting
3. The blood vessels.

Each of these structures must be considered in some detail.

1. *The chorionic epithelium*.—Great confusion existed for a long time regarding the nature of the epithelial covering of the villi, and the chorionic membrane generally. Although considerable progress has been made in clearing up disputed points, there are still some matters of the first importance which remain unsettled.

In a well-preserved specimen of a young placenta, it is easy to demonstrate the presence of a double layer of cells covering the villi and all other parts of the chorion (Plate XXI. Fig. 7). This double layer has been observed as early as the second week (¹⁸, ³⁸). After the mid-term of gestation marked changes occur, the deep layer disappearing more or less completely. The appearances, therefore, vary greatly at different periods, and to this circumstance a great part of the confusion which existed on the subject was due. Observers advanced different views,¹ for the reason that they based their observations upon specimens taken from different periods of development.

The superficial layer consists of a thin stratum of granular, multinucleated protoplasm, in which no cell outlines can be distinguished (Plate XXI. Fig. 7). The whole layer stains deeply; its nuclei are small, round, deeply-staining bodies, placed at irregular intervals; its protoplasm is in places prolonged between the underlying cells of the deep layer. This layer is now often called the syncytium, a term introduced by writers upon the comparative anatomy of the placenta.

In the deep layer the cells are large and well-defined, with oval nuclei standing with their long axes at right angles to the surface. The intranuclear network stains very distinctly. The perinuclear proto-

¹ In a recent work (⁶²), published since this paper was written, Dr. Clarence Webster has called this layer the trophoblast, a term which he has adopted from Hubrecht's work on the placentation of the hedgehog (¹⁶). Dr. Webster's description of the trophoblast in extra-uterine gestation, and that given here of the chorionic epithelium of the uterine placenta, are in all important respects identical.

plasm is often retracted from the nucleus. There is no basement membrane present (Plate XXI. Fig. 7).

There is now a complete agreement upon the existence of these two layers of cells, and their general characters. There has been, however, and still remains, the greatest difference of opinion upon their morphology. The following examples, which comprise the most important views which have been advanced, will serve to show the extent to which this divergence of opinion has been carried:—

1. Both layers of foetal origin; the superficial epiblastic, the deep mesoblastic. Langhans (²⁷).

2. The superficial layer of maternal origin, from the endothelium of the decidual vessels; the deep layer from the foetal epiblast. Winkler (⁴⁵).

3. Both layers of maternal origin; the superficial from maternal endothelium, the deep from maternal connective tissue. Tafani (⁴⁷).

4. Both layers of foetal origin, from the epiblast. Kastchenko (²⁸), Minot (³²).

5. The superficial layer of maternal origin, being a prolongation of the syneytium deciduae; the deep layer from the foetal epiblast. Ereolani (⁶), Turner (³⁹), Merttens (³¹).

This list is by no means exhaustive; some observers have found only a single layer of cells; others have found three; and all have constructed theories to account for what they found.

It is here unnecessary to discuss these theories in detail, and, inasmuch as it is impossible in the present state of our knowledge to come to a final conclusion, such a discussion would be of little service. My own observations do not bear upon the point, but, from a careful consideration of the work of others, I believe that there are no well-supported facts which point to the origin, in the human placenta, of either of these layers of cells from maternal structures. The superficial layer I regard as epiblastic; the origin of the deep layer is perhaps more doubtful, but there are, undoubtedly, certain facts which strongly suggest the mesoblastic origin of these cells. These facts were originally pointed out by Langhans (²⁷), and it is his view which seems to me to be most in accord with the facts as they at present stand.

In animals considerably more progress has been made in determining the origin of the cellular covering of the chorion. Several observers have proved that in the dog, cat, mouse, etc., the superficial layer is in reality a maternal tissue (⁴⁴). They trace the formation in the decidua of masses of deeply-staining multinucleated protoplasm, which they have named the syneytium. These plasmodia occur as isolated masses, or as large areas or tracts, and appear to be developed from decidual cells, or from surface or glandular epithelium. Their characters are identical with those of the superficial layer of the chorionic epithelium, and the syneytium may be traced passing in direct continuity from the decidua

to the surface of the villi. These observers, therefore, term the superficial layer the *syneytium*, and regard it as a maternal structure.

The only observers who have attempted to prove a similar origin of the superficial layer in the human placenta are Kossinmann (²⁴) and Merttens (³¹). Merttens' observations must be regarded, however, as extremely unsatisfactory. They were made upon a 16 days' ovum, obtained by curetting from a patient suspected of malignant disease of the uterus, who had suffered for some time from a profuse discharge. Observations made upon such unsuitable material as this can lead to nothing but confusion, and some caution must always be exercised in applying to the case of man the results of comparative anatomy. The question can only be satisfactorily settled by observations upon the human ovum in the earliest stages of development, and in a healthy condition.

Returning now to the structure of the chorionic epithelium, we find that during the early months the superficial layer shows great activity. Marked proliferation occurs in definite localised areas; this proliferation results in the formation of nodes or thickenings of various sizes, or of club-shaped or broad-based processes upon the epithelium. These nodes consist, like the superficial layer itself, of masses of nucleated protoplasm, in which cell outlines cannot be made out (Plate XIX. Fig. 3, and Plate XXI. Fig. 9). The deep layer appears to take no part in the formation of these buds, which are found most numerous upon the villi, but are present, in the earliest stages, in all parts of the chorion. In most of the buds the nuclei are crowded together in the centre, with a clear area of protoplasm surrounding them. Sections of processes are frequently seen as free islets of nucleated protoplasm in the intervillous spaces. Neighbouring buds often unite, forming a bridge across the intervillous space, and this process of fusion may go on to the formation of large areas, in which several villi lie embedded.

These appearances were at one time entirely mistaken. The free islets were regarded as sections of processes of decidual tissue growing into the placenta, the areas of fusion as large decidual processes in which villi had become embedded. And upon this interpretation was based the theory that the placenta developed by mutual ingrowth of foetal and maternal structures.

In point of fact, these proliferating areas represent the various stages and modifications of the process of budding, by which new villi are formed from the parent stems. The steps by which an epithelial bud becomes a vascularised villus can be readily traced in a young ovum, and are represented in Plate XIX. Fig. 3, and Plate XXI. Fig. 9, which are taken from an ovum of the sixth week. Small cavities first appear in the plasmodium, which enlarge, and fuse with neighbouring ones to form considerable rounded spaces. In the larger spaces blood may often be found (Plate XIX. Fig. 3 d), showing that they are in fact elementary blood channels. At first there is no definite

wall to the blood channel; it is bounded only by protoplasm. Next, a more or less complete ring of nuclei may be traced around it (Plate XXI. Fig. 9), and finally, a complete ring of rather large-celled endothelium is formed (Plate XIX. Fig. 3 D). In a large bud, two or three sections of blood channels may be found lying in the plasmodium without any trace of supporting connective tissue. Later, a delicate reticulated tissue appears around them, the nuclei of the plasmodium become arranged peripherally, forming the superficial layer of the chorionic epithelium, and the structure of the villus is complete. The connective tissue stroma appears to grow out into the bud from the parent villus (Plate XIX. Fig. 3 B). It seems probable that the vacuoles in the bud open into the meshes of the stroma of the parent villus; these meshes, as will be shown later on, contain abundance of free blood, which makes its way into the channels formed in the bud. These channels are not provided with definite walls until a later period, when the connective tissue grows into the bud.

All the epithelial buds which are formed do not become villi; large numbers of them undergo retrograde changes, which become of great importance in the structure of the full-time placenta, but need not be referred to here. At this period, too, the epithelium is much altered, the superficial layer has lost many of its nuclei, and is everywhere much thinned, and in places absent; the deep layer is represented only by clumps of atrophied nuclei, scattered here and there beneath the altered superficial layer.

The part played by the superficial layer of the chorionic epithelium in the formation of new villi is one of the strongest arguments in favour of the view that it is a structure of fetal, not of maternal origin. It is impossible to conceive of a tissue of maternal origin taking the initial and fundamental steps in the development of new villi from parent stems. Much greater importance must in any case be allowed to facts such as these, than to analogies drawn from comparative anatomy.

2. *The connective tissue stroma* forms the substance of the chorionic tree and supports the blood vessels. In a placenta of the second or third month it forms a delicate reticulated tissue, composed of nucleated masses of protoplasm, with numerous anastomosing processes (Plate XIX. Fig. 3, Plate XXI. Figs. 7 and 8). The nuclei are large, and the amount of perinuclear protoplasm is relatively small; the intranuclear network is very distinct. Leucocytes are present in large numbers at this period. The interstices of the reticulum appear to form a system of channels, probably of the nature of lymphatics, communicating with the capillaries; they can be injected artificially from the chorionic vessels, and red blood cells are sometimes detected in them. In the larger divisions of the chorionic tree the tissue becomes more compact; numerous spindle cells and connective tissue fibrils appear, especially in the neighbourhood of the vessels. In a placenta

at term, the whole stroma has become changed into the type of ordinary connective tissue, and the leucocytes have mostly disappeared.

3. *The chorionic vessels.*—The distribution of the branches of the umbilical vessels upon the surface of the placenta is well known and need not be recapitulated. The arterial branches dip suddenly from the foetal surface into the placental tissue; none of them reach to within half an inch of the margin. Upon the placental surface the arteries give off a number of minute twigs, which ramify in the sub-amniotic layer of the chorion, and with their corresponding veins form a complete circulation, whose function is the nutrition of the chorionic membrane, Holl (¹⁴). Beneath the surface they penetrate the placenta in a series of four or five terrace-like steps; they then branch repeatedly, and the branches do not anastomose. These branches pass into the ramifications of the chorionic tree, and terminate in the vascular loops of the villi. In the larger divisions of the chorionic tree the vessels lie in the axis; in the villi they are placed for the most part immediately beneath the epithelium, where they run a tortuous course and anastomose freely. It seems doubtful whether the loops in the villi are true capillaries, that is, channels of transition between arteries and veins; for in many instances the efferent vessel of one villus appears to become the afferent vessel of the next.

All these points may be made out in a normally shed placenta by injections of carmine-gelatine. Almost better results may be obtained by a simple device, which furnishes a natural injection of the vessels. The cord is tied at the moment of birth of the child, before respiration has aspirated the placenta. When the afterbirth has come away, the blood is squeezed back from the cord towards the placenta, and the cord is tied again at its point of insertion. The whole placenta is immersed in Müller's fluid for 24 hours; portions may then be cut out with very little escape of blood, and hardened by the usual method. Illustrations are shown of sections prepared by both of these methods (Plate XIX. Fig. 4, Plate XXI. Fig. 10).

A section of an injected placenta thus prepared shows, in the larger branches of the chorion, the axial vessels of large size, and numbers of small vessels lying peripherally, which form a superficial network; branches may be traced running off from the axial vessel to the surface. A delicate thread of injection may often be traced in the elementary vessels of the epithelial buds. In the villi of a carmine-gelatine injected placenta the meshes of the stroma are extensively injected, and this without any evidence of rupture of vessels having occurred (Plate XIX. Fig. 4). And in the naturally injected placenta red blood cells are frequently found lying in the meshes of the stroma of the villi. These appearances indicate the existence of a system of lymphatic channels in the stroma, communicating freely with the vessels of the villi. Small capillary twigs are often found, which appear to empty themselves directly into the stroma (Plate XIX. Fig. 4). The villi are therefore saturated with

blood like a soaked sponge. No escape of the injection into the intervillous spaces has ever occurred in my specimens. I have entirely failed to find any definite communication between the vessels and these lymphatics, although I am inclined to think that such must exist.

The minute structure of the vessels deserves some notice. In a young placenta from the third month the capillaries of the larger villi possess a layer of large-celled endothelium, almost cubical in type. In the small villi the tortuous capillaries always possess exceedingly delicate walls, consisting of a single layer of endothelium, supported directly by the connective tissue (Plate XIX. Fig. 4, and Plate XXI. Fig. 12). When they are full of blood, the capillaries appear to occupy nearly the whole of the villus. As a rule they run along the periphery, the only structure intervening between them and the intervillous spaces being the chorionic epithelium (Plate XIX. Fig. 4). In a full-time placenta many of the capillaries are actually exposed by the atrophy and disappearance of this covering. In the larger divisions of the chorion the vessels show some condensation of tissue around them, representing an attempt at the foundation of a tunica adventitia. The largest branches possess the usual three coats.

B. *The Maternal Placenta.*

The maternal elements of the placenta are developed from the uterine mucous membrane. The steps by which the normal mucous membrane is converted into the decidua have now been clearly made out. It must be remembered, however, that the fertilised ovum is not engrafted upon the mucosa in a state of quiescence, but as altered by the process of menstruation, that is, in a state of activity. It is now possible to give an outline, at anyrate, of the changes which occur in the uterine mucous membrane of the human subject during menstruation.

The earliest change in menstruation is hyperæmia and swelling of the mucous membrane, associated with hyperplasia of its connective tissue elements. The glands become dilated and contorted, and their epithelium proliferates; the connective tissue elements multiply, and, according to some, a marked infiltration of the stroma with leucocytes occurs. No trace is, however, found of the large decidual cells so well known in connection with pregnancy. Hæmorrhages occur in the superficial layers, but whether from actual rupture of capillaries is not made out; it is, however, certain that no considerable vessels rupture. In consequence of these hæmorrhages the superficial layers are broken up and cast off along with the covering epithelium. It is probably at this moment that the fertilised ovum, reaching the uterus becomes engrafted upon the altered mucous membrane.

This account, based upon observations on the human uterus, may be supplemented by the recent researches of Heape into the menstrual phenomena of *Simnopithecus entellus* (⁴⁸). In these monkeys Heape

has made out that a definite increase in size and number of the vessels occurs in the superficial layers of the mucosa, and that the dilated vessels, probably capillaries, rupture and form small hæmorrhages beneath the epithelium. Later, the extravasated blood collects in lacunæ, formed by destruction of the connective tissue, which in time burst through the epithelium, and allow the blood to escape into the uterine cavity. The rupture of the vessels is probably due to (1) thinning of their walls (2) diminished support of surrounding tissues, (3) some undetermined form of degeneration affecting their walls.

If a fertilised ovum does not reach the altered mucous membrane, the stage of activity subsides, and the damage done is probably soon repaired, the epithelial layer being regenerated from the glandular epithelium which remains. Under the stimulus of the presence of a fertilised ovum, however, the mucous membrane enters upon a new career, and becomes the decidua of pregnancy.

The changes which occur in the formation of the decidua may, for convenience, be divided into three stages:—

The first stage is characterised by the development of decidual cells, and the occurrence of extensive hæmorrhages in the mucosa. The decidua vera, reflexa, and serotina show the changes characteristic of this stage.

The second stage affects the serotina only. It consists in the invasion of the serotina by the chorionic villi, and the opening up of the maternal vessels, by which the circulation through the intervillous spaces becomes established.

The third stage represents the adult phase, in which the serotina consists of two distinct layers—a superficial compact, and a deep cavernous layer.

After the completion of the first stage the vera and reflexa undergo retrograde changes.

First stage.—In the first stage the decidua differs from the mucous membrane of menstruation in two essential particulars—first, in the presence of large numbers of large, round, nucleated cells, known as the decidual cells; and, secondly, in the widespread occurrence of dilatation and rupture of the vessels.

The decidual cells may be considered to be characteristic of pregnancy. It is certain that they do not occur during menstruation. Similar cells have, however, been observed by Overlach (⁴⁹) in acute phosphorus poisoning, and by Calderini (⁵⁰) as the result of experimental irritation of the uterus in animals. Pregnancy is, however, the only instance in which they occur under normal conditions. The characters of decidual cells are too well known to need recapitulation. Their development from connective tissue corpuscles has been repeatedly observed—Hart and Gulland (¹⁵), Minot (²²), Bumm (⁵)—and may be readily traced in a young ovum. The stages by which the spindle cell becomes the large round decidual cell are presented *ad naturam* in

Plate XIX. Fig. 1. Transition forms of every shape and variety may readily be found. They generally show a single, large oval, deeply-staining nucleus; at times there are two nuclei, very rarely three. In almost all parts red blood corpuscles are found lying singly or in heaps among the decidual cells.

The presence of giant cells in the decidua has been known for many years; they are generally supposed to be developed from decidual cells by a process of nuclear division. I am convinced that this is incorrect, and that the so-called giant cells are in reality sections of epithelial buds from the chorionic villi, which have become embedded in the decidua. This point will, however, be referred to more fully later on.

The small vessels are all markedly dilated, and their walls thinned. These changes are most marked towards the surface, where many vessels have ruptured, with extravasation of blood into the decidual tissue. The blood poured out breaks up the surrounding tissues, and finally makes its way out into the free space between the chorion and the decidua. Some of the hæmorrhages in the decidua are of large size, and often considerable extravasations into the intervillous spaces are found at the end of the first month. These changes, representing the first stage, are mainly preparatory, and are probably completed towards the end of the first month. They occur alike in the decidua vera, reflexa, and serotina; the second and third stages, however, are limited to the serotina.

Second stage.—The period during which the changes, characteristic of the second stage, occur cannot be exactly defined. They probably commence about the end of the first month: round the growing margin of the placenta they may continue until the last weeks of gestation, although in the more central parts they are completed earlier. They are in fact progressive and contemporaneous with the period of growth of the placenta itself.

There has been great difference of opinion expressed about the development of the serotina, and it is impossible, within the limits of this paper, to review the many theories that have been advanced. I shall, therefore, only refer to results which have been satisfactorily confirmed.

The changes which occur in the serotina are due to the remarkable activity of the chorionic villi. Wherever the placenta is growing the process of proliferation by budding, already described, goes on actively in the villi. These also invade the serotina, break up its tissues, and bore through the walls of its vessels. In this manner the maternal circulation through the intervillous spaces becomes established.

A section of the serotina at the beginning of the second month is shown in Plate XX. Fig. 5. The dilated and turgescient state of the vessels is very striking. Hæmorrhages into the tissue are seen at Hæm. At Gld. is shown a section of a dilated gland, well preserved, although detached, cubical epithelium: in many sections of glands the epithelium

is markedly proliferating. The decidual cells are loosely arranged, and in places there are masses of small round cells among them. The tissue is in parts extensively broken up by hæmorrhage; many of the glands contain blood (Plate XX. Fig. 6, Plate XXI. Fig. 11), and some of them are seen to communicate by a rupture with a neighbouring hæmorrhage (Plate XX. Fig. 6). In this manner irregular cavities full of blood are formed by rupture of vessels, and opening up of the surrounding decidual tissue.

In the neighbourhood of the hæmorrhages the decidual cells are seen to be actively engaged in absorbing blood (Plate XX. Fig. 6). Some of them contain only a small quantity of blood in the perinuclear protoplasm. Others are full of blood, and in these the nuclei are more deeply bloodstained than the protoplasm. The glandular epithelium may also, in the same way, be found absorbing the blood effused into the gland channel (Plate XX. Fig. 6). This process is probably an attempt at repair, on the part of these active cells. I am not aware that it has been described in the human serotina before.

It has been already stated that maternal blood becomes effused into the intervillous spaces as early as the end of the first month. This blood is to some extent reabsorbed by the chorionic epithelium (Plate XX. Fig. 6). The proliferating epithelium covering the villi, and the epithelial buds, are equally active in this respect. This process has been described by Strahl⁽⁴⁴⁾ as occurring in the placenta of the bitch. It has no nutritive significance, but is merely a method of disposing of what is practically a foreign body. There is no effective circulation through the intervillous spaces at this period, and blood effused into them represents practically an interstitial hæmorrhage.

Masses of small round cells are often found in the neighbourhood of the serotinal hæmorrhages (Plate XX. Fig. 5). Some of them are, no doubt, leucocytes, but very many arise from the decidual cells by a process of division. The transition stages of this process are represented *ad naturam* in Plate XIX. Fig. 2. These cells are probably concerned in the absorption of blood, and in the process of repair.

This is the condition in which the serotina is found at the period in which the villi begin to invade it. For many years the view first advanced by Turner (*loc cit.*) was maintained, that the villi penetrate the serotina by entering the open mouths of the dilated glands. It is now agreed that this is an error. Early in the second stage the mouths of the glands become closed, although the deeper dilated portions remain until the end of gestation. The villi bore their way directly into the serotinal tissues.

The process of penetration appears to depend upon the activity of the epithelial buds. In Plate XX. Fig. 6 are seen a number of sections of buds which have buried themselves in the serotina; the specimen is from the middle of the second month. By the steps which have been previously described, the bud becomes a villus, from which in

turn fresh buds arise. There is no evidence that fully formed villi push their way into the serotina by growth from behind. In this manner, first the superficial layers, and then the deeper ones, are invaded by the villi. Plate XX. Fig. 6 shows a deeply situated hæmorrhage in which a villus is embedded, and around it are numerous sections of epithelial buds, arising from other villi which do not appear in the section. Those parts of the serotina, which are thus invaded by the villi, become excavated; already disintegrated by hæmorrhage they now become entirely broken down, and thus pits or depressions are formed upon the serotinal surface.

This process of excavation results in the formation of an irregular series of elevations and depressions upon the surface of the serotina. It is found that the arteries open upon the elevations, while the veins open upon the intermediate depressions, Bunum (⁴), Ahlfeld (¹). No one seems yet to have definitely proved that the arteries are opened up by the villi penetrating their walls. There remains, therefore, the possibility that the arterial capillaries rupture from the force of the blood current, assisted by thinning of their walls, and loss of support from surrounding tissues. An opening once made tends continually to enlarge by the action of the outflowing blood upon the loose decidual tissue. Villi cannot enter the channel against the blood current; the openings of the arteries are, therefore, always clear of villi, which are washed away from its immediate neighbourhood. The walls of the veins, on the other hand, are probably broken through by the villi. The direction of the blood stream favours their penetration, and venous channels can generally be distinguished by the fact that they contain sections of villi or epithelial buds. By the end of the second month there is probably a definite circulation through the intervillous spaces.

It is at this period that the so-called giant cells have been described as appearing in the placenta. I believe that these cells are, in reality, sections of epithelial buds. They have been described as present in all parts of the serotina; but especially in the deeper parts, and in the venous channels. It is in precisely these parts that the epithelial buds are most numerous. Structurally, the buds are merely multinucleated plasmodia, and so are giant cells. The only question is, therefore, as to their origin. After a very careful search I could find no evidence of the formation of giant cells from decidual cells, while their origin from the chorionic epithelium has been already demonstrated in Plate XIX. Fig. 4 and Plate XXI. Fig. 8. I am, therefore, inclined to believe that they are, in reality, foetal structures.

As a result of the excavation of the serotina, which occurs at this period, small portions of decidual tissue appear at times to become detached, and carried into the intervillous spaces by the blood current. They may even be found immediately beneath the chorionic membrane. They become moored to one or more of the villi, and later on undergo retrograde changes, which are of considerable importance in connection

with the formation of the white placental infarct. This matter does not, however, come within the scope of the present paper.

When the intervillous circulation has been established, no further active changes occur in the serotina at that part. Round the growing placental margin, however, changes characteristic of the second stage may be found up to the last weeks of gestation.

The process by which the placenta increases in size deserves a moment's consideration, and this is perhaps the most convenient place at which to refer to it. The growth of the placenta is intimately associated with the development of the decidua reflexa. It is now agreed that the reflexa is formed by a splitting of the vera around the base of attachment of the ovum. The superficial layer, containing numerous vessels and glands, grows up around the ovum and encloses it. The reflexa is, therefore, the superficial layer of the vera reflected over the ovum. It is nourished by vessels which enter its base from the vera. It is thickest in the parts nearest its junction with the vera, and towards the free pole of the ovum it thins gradually away; this thinning being probably brought about by the pressure of the growing ovum, and the distance of the part from the source of blood supply. As the ovum grows the reflexa is carried with it and thus becomes raised from the vera over a continually increasing area. In this manner room is provided for the peripheral growth of the placenta. This growth is at first very rapid. At the end of the second week the base of attachment of the ovum is equal in area to about one-fifteenth of the total uterine surface. By the end of the third month the placenta occupies one-fourth of the total uterine surface, and this proportion is maintained up to the end of pregnancy. That is to say, after the third month, the growth of the placenta is only proportional to that of the entire uterus. After the third month, too, the functions of the reflexa cease to be of importance; the growth of the ovum has overtaken that of the uterus and fills it entirely, and the reflexa atrophies from constant pressure.

Glycogen has been found by Merttens ⁽³¹⁾ and others in the glandular epithelium and in the decidual cells of the serotina. It is contained in fairly definite areas of the periphery of these cells. The presence of glycogen in the placenta was discovered by Claude Bernard ⁽⁵¹⁾, but I am not aware that it has been precisely localised before. I have not been able to find glycogen in any of my specimens, and I am, therefore, inclined to believe that its presence is not constant.

Third stage.—By the time that the intervillous circulation is established the placenta has assumed its adult form. The serotina now undergoes some measure of consolidation and repair. The hæmorrhages become to a great extent cleared up, although blood corpuscles may in parts be found among the decidual cells at the mid-term of gestation. The decidual cells become more closely packed, forming an altogether denser type of tissue than that of the earlier stages. Villi are unable

to penetrate it for any considerable distance, but they become attached in large numbers to its surface.

Even at the beginning of pregnancy the decidua is roughly divisible into two layers: a superficial layer, in which the hæmorrhages are most numerous, and a deep layer containing the dilated glands. In the third stage, however, the serotina consists of two perfectly distinct layers: a superficial compact layer, and a deep cavernous layer (Plate XXI. Fig. 12). *The superficial layer* is composed of closely-packed decidual cells, and is traversed by the placental arteries and veins, which open upon its surface into the intervillous spaces. There are no glands in this layer. The surface is covered by a stratum of fibrin. *The deep or cavernous layer* contains a network of irregular, dilated, glandular channels. In the third and fourth months, many of the glands retain a well-preserved lining of cubical epithelium. Towards the end of pregnancy, only occasional small groups of these cells remain; so that the channels are often mistaken for veins. The arteries and veins, of course, also pass through it. The decidual stroma consists of cells smaller and more closely packed than those of the superficial layer. It is through the deep layer that separation of the placenta occurs when it is normally shed.

The course of the maternal vessels deserves more detailed notice. The fact that these vessels opened into the intervillous spaces was proved long before the details of the process by which this communication becomes established were worked out. Waldeyer⁽⁴³⁾ first succeeded in making satisfactory observations upon this point, and his research is one of the landmarks of the study of the placenta. Very little has since been added to his description of the course of the maternal vessels in the adult placenta.

There are very few capillaries in the serotina at this period; the arteries and veins open directly into the intervillous spaces, but before doing so they give off a few nutritive branches to the serotina. The arteries run a spiral course right through the uterine wall. In many naturally shed placentæ, the torn ends of these arteries may be detected upon the maternal surface. In the muscular wall of the uterus, they show the usual three coats, and round many of them is found a semi-circular, peri-lymphatic space. When the artery leaves the muscular wall the middle coat disappears, and in the serotina there is only an endothelial layer surrounded by a loose fibrous sheath. The artery enters the serotina vertically, but alters its course so as to open obliquely into the intervillous spaces. The fibrous sheath ceases abruptly just before the artery opens. Waldeyer asserts that the endothelial layer may be traced not only up to the opening, but for some distance over the surface of the adjacent serotina. Others believe that it disappears with the fibrous sheath, so that the actual aperture is formed only by the rounded edges of the decidual tissue (Plate XXII. Figs. 15 and 16).

The veins form large sinuses in the muscular wall of the uterus.

On reaching the serotina their course is nearly parallel to its surface, they then rise gradually and so open very obliquely into the intervillous spaces.

We are now in a position to refer to the vexed question of the origin of the intervillous spaces. In the first place, the boundaries of the general intervillous space should be pointed out. Towards the uterus it is limited by the serotina; towards the fœtus by the chorionic membrane, from which the villi arise; at the placental margins by a reflection of the serotina beneath the chorionic membrane. The placental margin represents the line of union of the three parts of the decidua; the decidual tissue is here especially thick, it supports the circular sinus and contains numbers of embedded villi. It is prolonged into the placenta beneath the chorionic membrane for 1 to 2 inches, thinning out gradually as it passes inwards.

The question at issue has been, Are the intervillous spaces altered maternal vessels or not? The solution has been sought in the direction of determining whether the spaces are entirely enclosed in tissue of maternal origin, that is, whether or not the villi receive an investment of maternal tissue. Among the earliest advocates of the view that the intervillous spaces are maternal were Turner and Ereolani. They based their theory upon the opinion they had formed that the villi of the adult placenta possessed a complete investment of maternal tissue; the intervillous spaces could then quite properly be regarded as altered maternal blood vessels. They did not attempt, however, to establish their views by tracing the development of these spaces. Somewhat the same theory has been revived in a different form by Waldeyer, and also by Keibel. These observers believe that they have found a delicate layer of endothelium covering the villi, which they hold to be the representative of the walls of dilated maternal capillaries. Keibel's observations (¹⁸) are so incomplete that little importance can be attached to them. Waldeyer's observation, therefore, stands alone, and it is important to remember that it derives no support whatever from the facts which have been established in regard to the beginnings of the placenta. More recently still, Kossmann and Merttens (*loc. cit.*) have attempted to return to the theory of Turner and Ereolani by applying the facts of comparative anatomy to the human placenta. Reasons have, however, already been given for suspending judgment upon this point for the present.

The methods by which these theories have been arrived at are open to objection. The question cannot be solved by observations upon the adult placenta (that is, upon the placenta in the second stage), supplemented by theories accounting for what is then found. The facts can only be arrived at by tracing in detail the steps by which the intervillous spaces are formed; when this is satisfactorily accomplished their origin is no longer a matter of theory but of fact. An attempt is made in this paper to describe the changes in the placenta which result in the formation of these spaces. These changes occur, however, at a very

early period when it is difficult to obtain material in a condition suitable for examination, and further observations are, no doubt, needed. But if the account given here be correct, then the intervillous spaces are not dilated maternal capillaries, nor are they spaces enclosed in maternal tissue at all; they are made up as follows:—

1. By the space primarily existing between the decidua and the chorion;
2. By spaces formed by destruction and absorption of decidual tissue;
3. By glandular and vascular maternal channels, opened up in the same way.

In the spaces thus formed the villi develop, and many of them become attached to the serotina. They are in direct contact with the maternal blood, which circulates among them. This arrangement seems in all respects admirably adapted to promote osmotic interchanges between the foetal and maternal blood, the chorionic epithelium representing the dialyser. This osmotic interchange is the essential condition of the nutrition and development of the foetus. Very few facts, however, are known regarding the details of the process.

The circulation through the intervillous spaces is probably not a rapid one. This is an advantage in giving time for the occurrence of the osmotic changes. The spiral course of the arteries tends to considerably reduce the force of the blood stream, a modification which is probably necessary in view of the delicacy of the placental structures. The outflow from the spaces is chiefly promoted by the intermittent uterine contractions, which have the effect of aspirating the contents into the veins.

During the third stage villi are always found attached to the surface of the serotina, and some are embedded in it. The embedded villi are devascularised and functionless. When a villus becomes attached to the serotina, it loses first its superficial epithelial layer along the line of contact. The cells of the deep layer are then brought into contact with the decidual cells, and a marked proliferation of the deep layer occurs, so that a considerable area of round cell infiltration is formed around the site of attachment (Plate XXII. Fig. 13). This has the effect of welding the villus to the serotina. The process was first described by Langhans (²⁷), and he regarded it, as it seems to me, rightly, as evidence of the mesoblastic origin of the cells of the deep layer of what is called the chorionic epithelium. At times the proliferation of the deep layer is so extensive as to form a considerable layer of round cells lying upon the surface of the serotina. The superficial layer of the chorionic epithelium is generally prolonged from the sides of the attached villus over the adjacent serotinal surface for a short distance, but it does not form anything like a continuous layer (Plate XXII. Fig. 14). The death of the embedded villi at this period is due to the fact that they find, in the compact decidual tissue, none of those condi-

tions essential to their nutrition which are present in the earlier stages.

I have endeavoured in this paper to deal only with those changes and processes by which the human placenta is carried to its highest point of development and functional activity. The placenta at term is an overripe and decadent structure. Many changes are found in it which can only be regarded as degenerative, and these are left over for consideration in a subsequent paper. Among the matters thus left over, it is perhaps necessary to mention the subject of the origin of the substance known as canalised fibrin, which plays such an important part in the structure of the placenta at term. I believe the appearance of this substance to be the direct result of degenerative changes, and it has therefore not entered into the scope of the present paper. It is referred to now merely to avoid misconception.

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DESCRIPTION OF PLATES XIX. TO XXII.

PLATE XIX.

FIG. 1.—Represents the development of decidual cells from connective tissue corpuscles. The different forms are all drawn from the section represented in Figs 6 and 7. (Leitz, Oc. 3, Obj. 7.)

- a. Connective tissue corpuscles.
- b. Intermediate forms.
- c. Decidual cells.

FIG. 2.—Represents the formation of small round cells from decidual cells by fission. (Leitz, Oc. 3, Obj. 7.)

- a. Decidual cells.
- b. Cells in various stages of division.
- c. The resulting small round cells, many of them closely resembling leucocytes.
- d. Further division of the small round cells.
- e. Free nuclei.

FIG. 3.—Illustrates the process of budding and formation of new villi. The sections are from a complete ovum at the sixth week. (Leitz, Oc. 3, Obj. 7.)

A. Section of villus.

S.L. Superficial layer of the chorionic epithelium; the deep layer is not seen, it is often absent in young villi.

Ep. bud. Epithelial bud, springing from the superficial layer.

St. Stroma of villus.

- B. Section of a rather larger villus than A. Two epithelial buds are here shown; into the lower one the connective tissue stroma is prolonged.
- C. Horizontal section of an epithelial bud. There are two vacuoles present, and the nuclei are arranged roughly round the periphery.
- D. Horizontal section of a bud further developed than C. There is a section of a vessel near one end, with a distinct wall, and containing blood in its lumen.

FIG. 4.—From a placenta of the seventh month, injected with carmine-gelatine, by means of a tube and funnel. The section is stained with logwood. (Leitz, Oc. 3, Obj. 7.)

Cap. Capillaries filled with injection; they run for the most part immediately beneath the epithelium of the villus.

St. Stroma of the villus saturated with the injection; the nuclei and the protoplasmic network are uninjured, the injection being contained in the meshes.

T. Small twig springing from a capillary, and opening into the meshes of the network.

End. Endothelial cells representing the capillary wall.

PLATE XX.

FIG. 5.—Vertical section through the decidua serotina at the sixth week. From the same specimen as Fig. 3. (Leitz, Oc. 3, Obj. 3.)

D.C. Decidual cells.

R.C. Clusters of small round cells.

Cap. Distended capillaries, some of which have ruptured.

Hæm. Hæmorrhage into the decidual tissue.

Gld. Section of a gland, with cubical epithelium.

Art. Arterioles.

FIG. 6.—Shows the penetration of the villi into the decidual tissues. From the same specimen. (Leitz, Oc. 3, Obj. 3.)

D. Decidua.

V. Section of a villus embedded in a hæmorrhage.

Hæm. Hæmorrhages.

Ep. buds. Sections of epithelial buds from other embedded villi, not shown in the section.

(*a*) (*a*). Buds showing sections of vessels in their interior.

PLATE XXI.

FIG. 7.—From a three months' placenta, showing the two layers of the chorionic epithelium, and the protoplasmic network of the villus stroma.

FIG. 8.—From a six weeks' ovum. Villus showing the proliferation of the chorionic epithelium and an clougated epithelial bud.

FIG. 9.—From a six weeks' ovum. Shows the epithelial covering of the chorionic membrane, which is budding in places, and the proliferation of its nuclei. Two large epithelial buds appear in section, one of which contains two vessels, the other, one.

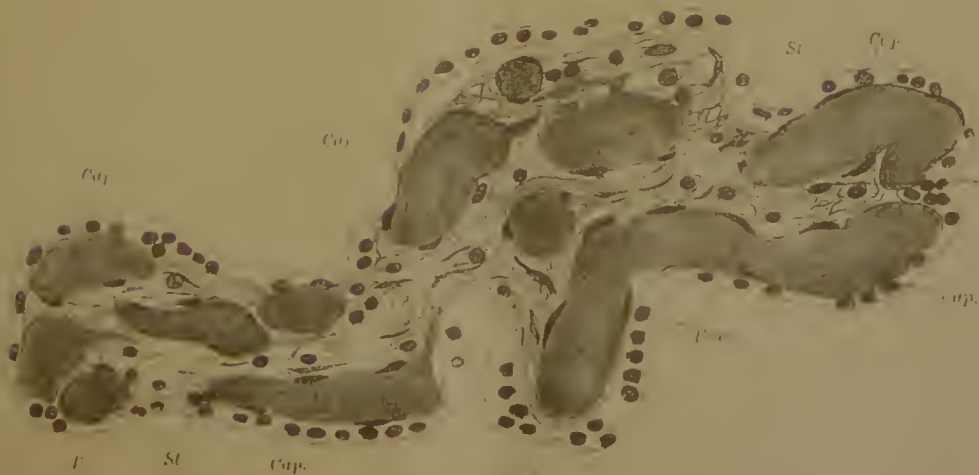
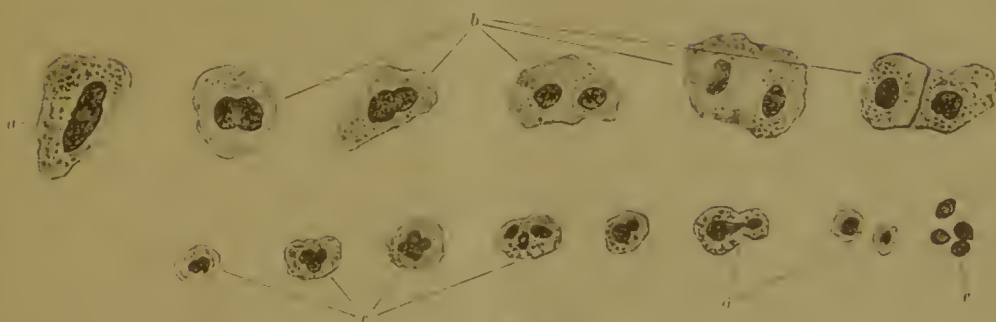
FIG. 10.—From a nine months' placenta, in which the foetal blood had been retained (natural injection). The villus in section shows several large capillaries packed with blood, and many sections of smaller ones scattered through the stroma.

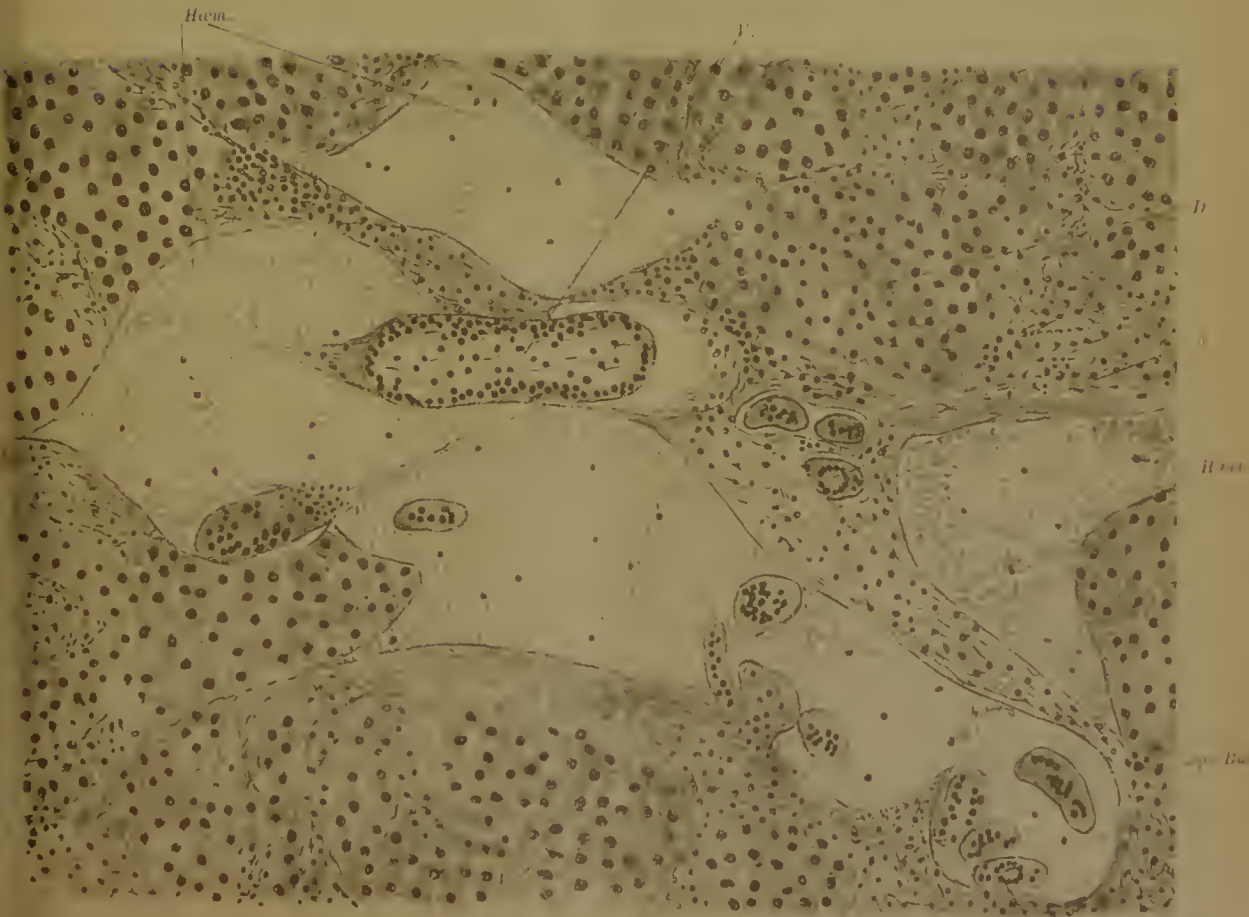
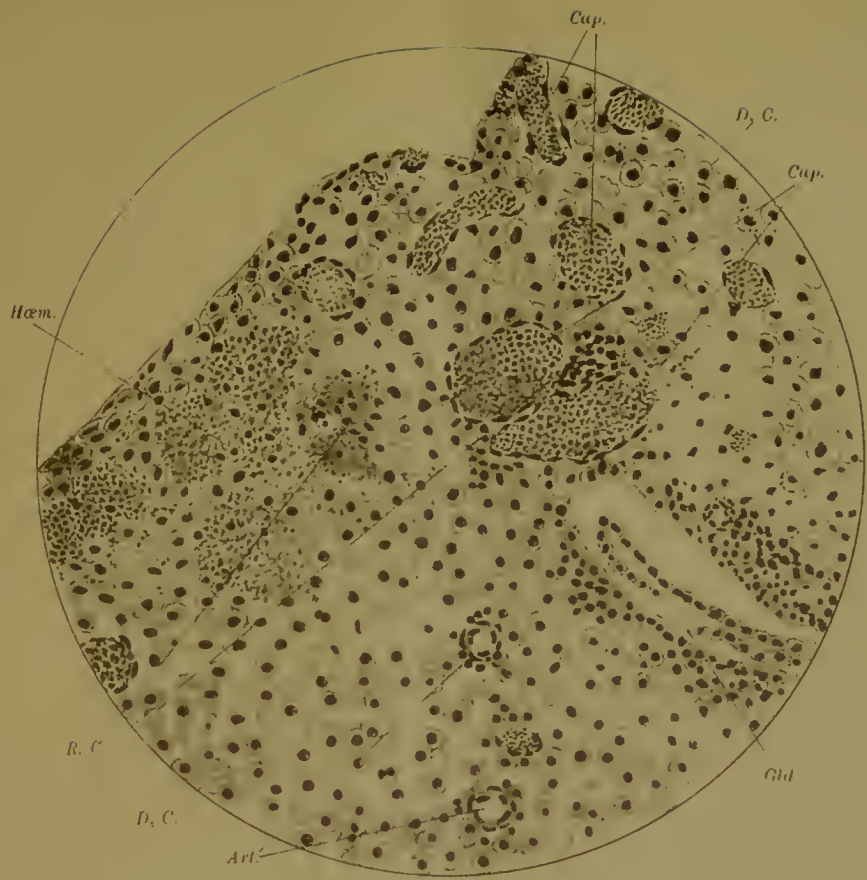
FIG. 11.—From a six weeks' ovum. The section is through the deeper part of the decidua serotina. Several glands are shown, containing blood, in the lower part of the figure; a large hæmorrhage occupies the upper part. At the margin of the hæmorrhage is a large epithelial bud with two vessels in section.

FIG. 12.—From a seven months' placenta. The figure shows the two layers of the serotina at this period; the dark band along the surface is composed of canalised fibrin.

PLATE XXII.

- FIG. 13.—From a three months' placenta. Shows a section through an attached villus, and the adjacent serotina. Along the line of attachment the epithelial covering is indistinct; its nuclei have proliferated markedly, and invaded the adjacent decidua tissue. At the right of the figure the superficial layer of the epithelium is seen to be prolonged for a short distance upon the serotinal surface.
- FIG. 14.—From the same placenta. Shows the serotinal surface with an interrupted layer of chorionic epithelium upon it.
- FIG. 15.—From the same placenta. Shows a maternal vessel in section, on the point of opening, at the apex of a decidua elevation, into the intervillous spaces.
- FIG. 16.—No. 4 of the series of sections, of which Fig. 15 is No. 1. Shows a point where the maternal vessel has opened in two places into the intervillous spaces.







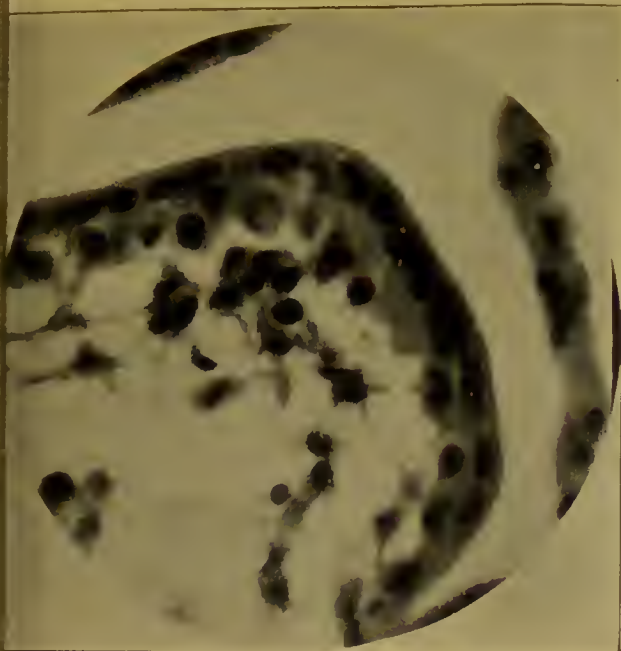


FIG. 7.



FIG. 8.

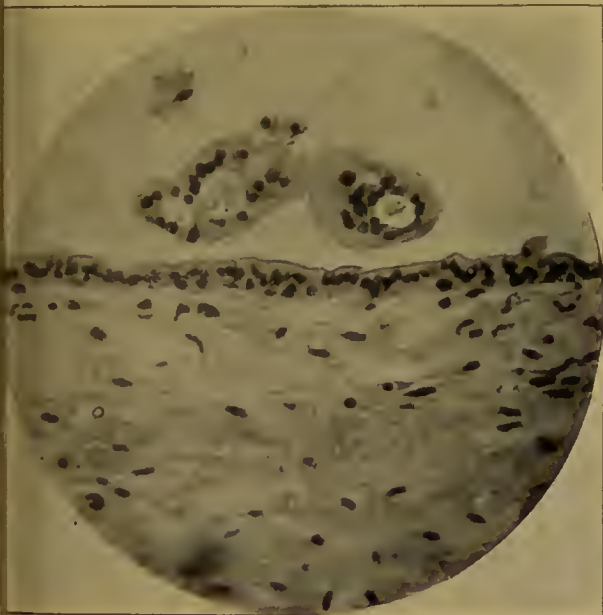


FIG. 9.

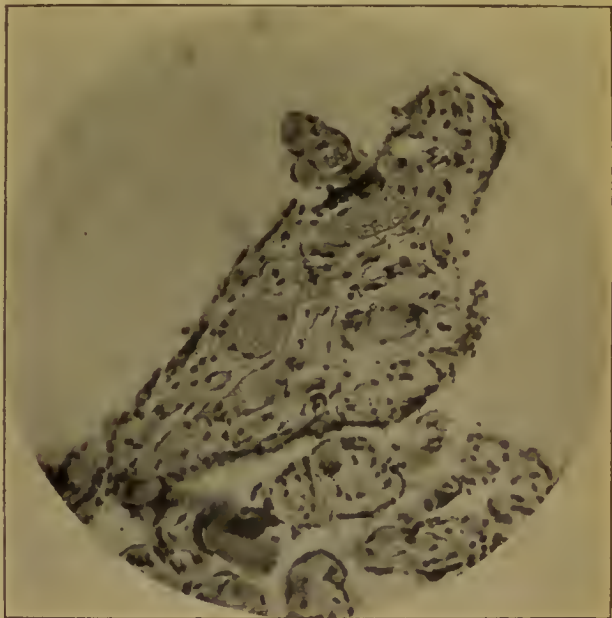


FIG. 10.

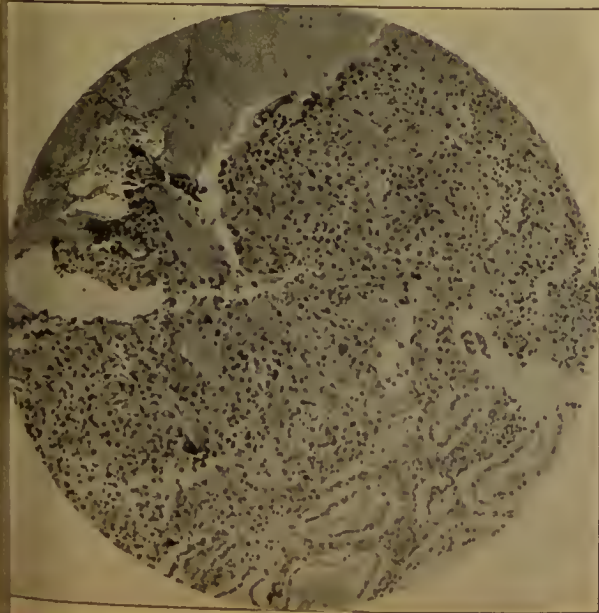


FIG. 11.

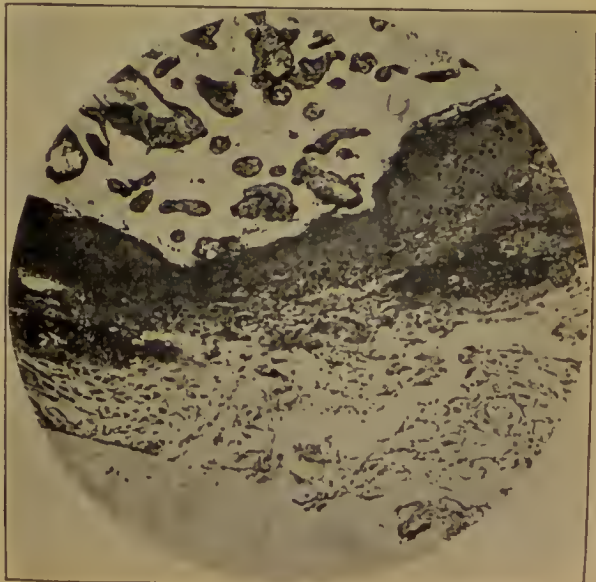


FIG. 12.

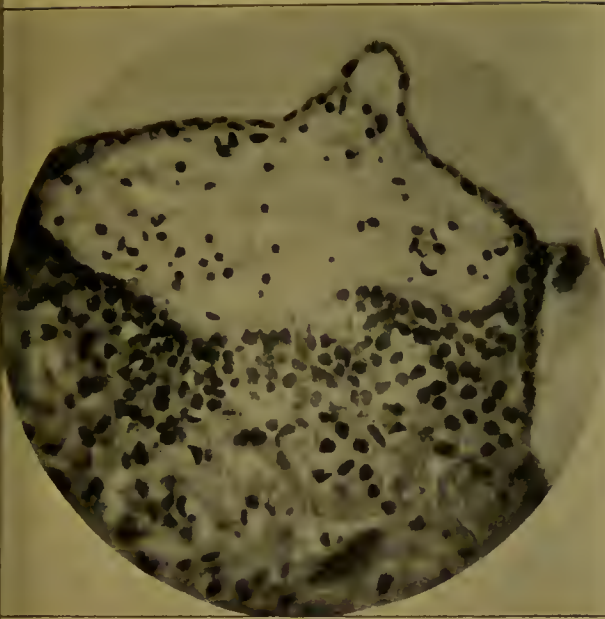


FIG. 13.

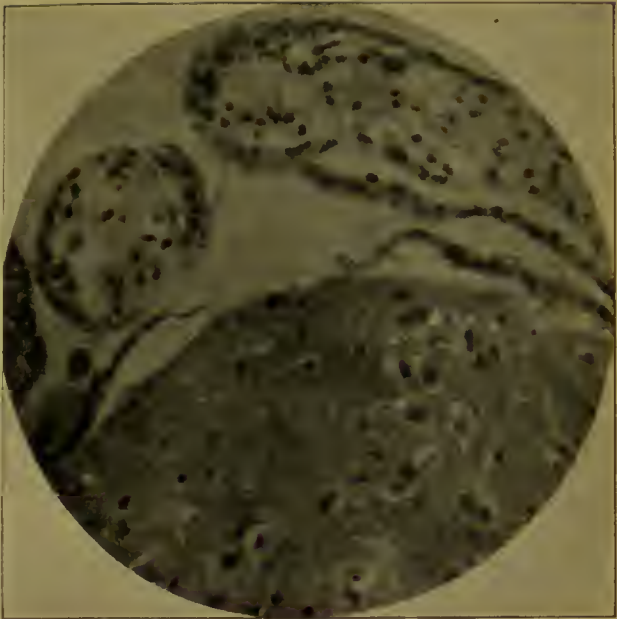


FIG. 14.

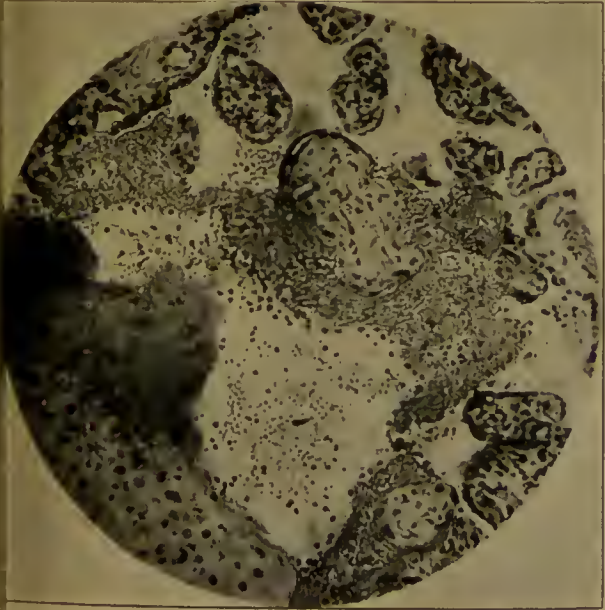


FIG. 15.

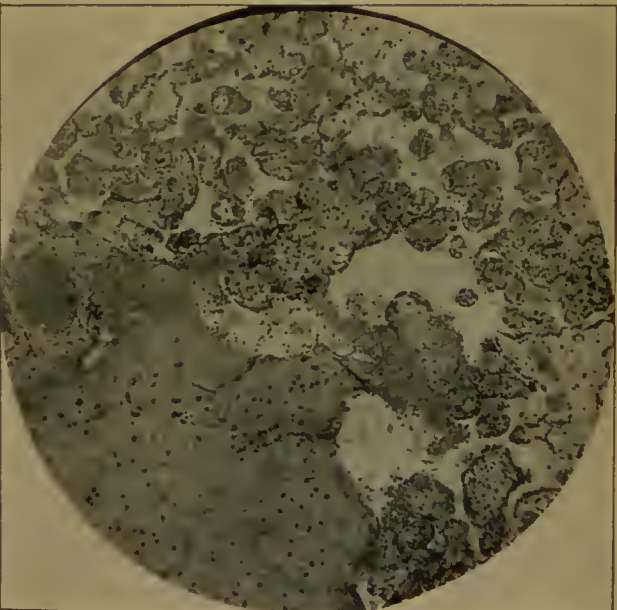


FIG. 16.

